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PATENT SPECIFICATION

Inventor: COLIN LESLIE HEWETT

719,402

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COMPLETE SPECIFICATION

A new and improved Cyclopentanopolyhydrophenanthrene Derivative and Methods for its Production

We, ORGANON LABORATORIES LIMITED, a British Company, of Brettenham House, Lancaster Place, London, W.C.2, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new and improved cyclopentanopolyhydrophenanthrene derivative and method for its production and it is particularly concerned with the production of a biologically active testosterone, derivative, having both a longer duration of biological activity and also a higher degree of activity than known derivatives.

In previous attempts to produce testosterone derivatives having a longer duration of activity than the commonly used simple esters, such as the propionate, benzoate or phenylacetate, it has been proposed to utilise the cyclopentylpropionate and the cyclohexylpropionate.

It has now been found that outstandingly successful results are obtained by the hitherto unknown testosterone β-phenylpropionate. It has been found by experiment that this substance maintains its action for a much longer period than the simple esters and at least to the same extent as the cyclopentylpropionate or cyclohexylpropionate derivatives and in addition it somewhat surprisingly exhibits a high degree of activity than either the simple esters and at least to the same extent as the cyclopentylpropionate and cyclohexylpropionate derivatives. Thus, for example, the growth of seminal vesicles in castrated rats obtained by injecting testosterone β-phenylpropionate is approximately equal to that obtained by injecting four to five times the weight of the propionate and the duration of activity is three or four times as long.

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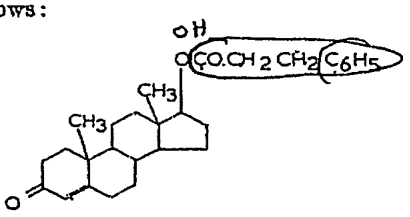
The new derivative according to the invention can be prepared by condensing testosterone with β-phenylpropionic anhydride either alone, in which case the reaction time is shortened by heating to a temperature of the order of 100° C., or dissolved in pyridine, benzene or other inert solvent. It can also be prepared by means of β-phenylpropionyl halide dissolved in an organic acid-acceptor such as pyridine or a mixture of benzene and pyridine containing sufficient pyridine to neutralise the hydrogen chloride liberated.

The structural formula of the new compound, testosterone β-phenylpropionate, according to the invention is as follows:



The following examples illustrate several methods of producing the new derivative according to the present invention.

EXAMPLE 1.

A solution of 10 gms. of testosterone in 30 cc. of pyridine is cooled in ice and 7.5 gms. of β-phenylpropionyl chloride added slowly with stirring. The solution is then removed from the ice bath, left at room temperature (15—20° C.) overnight and then the excess phenylpropionyl chloride is decomposed with ice. The solid ester is recrystallised from methanol; melting point 116—117° C.

EXAMPLE 2.

A solution of 10 gms. of testosterone in 30 cc. benzene and 10 cc. pyridine is cooled in ice and 7.5 mgs. β-phenyl-

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propionyl chloride added dropwise with stirring. The solution is then removed from the ice bath, left overnight at room temperature (15—20° C.) and then washed with water, dilute sodium carbonate solution and then dilute hydrochloric acid solution. The benzene solution after drying is distilled to dryness and recrystallised from methanol; melting point 116—117° C.

EXAMPLE 3.

To a solution of 10 gms. of testosterone in 30 cc. pyridine is added 12.5 gms. of β-phenylpropionic anhydride. After standing overnight at room temperature the excess anhydride is decomposed by addition of water, and the testosterone β-phenylpropionate crystallised from methanol; melting point 116.5—117° C.

EXAMPLE 4.

To a solution of 10 gms. of testosterone in 30 cc. benzene is added 15 gms. of β-phenylpropionic anhydride. After standing at 15—20° C. for twenty-four hours the solution is shaken with water and then dilute sodium carbonate solution, dried and distilled to dryness. The produce is crystallised from methanol, melting point 116—117° C.

EXAMPLE 5.

10 gms. of testosterone and 12.5 gms. of β-phenylpropionic anhydride are heated together at 100° C. for five hours. The melt is then triturated with water and the solid washed with dilute sodium carbonate solution, dried and crystallised from methanol, melting point 116—117° C.

The following table gives a comparison of the properties of the new testosterone derivative according to the invention, with the already known testosterone propionate derivative. The table shows the mean seminal vesicle weights (in mgms.) at various intervals after a single intermuscular injection of 0.1 cc. into castrated rats; the results for a range of comparative injections (I to V) being given. The different injections listed are prepared as follows:—

Injection I:—Testosterone propionate in sesame oil 2.5 mgm. in 0.1 cc. oil.

II:—Testosterone β-phenylpropionate in sesame oil 2.5 mgm. in 0.1 cc. oil.

III:—Testosterone propionate in ethyl oleate 2.5 mgm. in 0.1 cc. of the oleate.

IV:—Testosterone β-phenylpropionate in ethyl oleate 0.5 mgm. in 0.1 cc. of the oleate.

V:—Testosterone β-phenylpropionate in ethyl oleate 2.5 mgm. in 0.1 cc. of the oleate.

TABLE.

	3 days	5 days	7 days	9 days	14 days
Injection I	23.4	32.9	36.7	32.6	30.4
Injection II	33.2	48.1	91.4	120.2	76.8
Injection III	29.6	50.6	69.1	72.1	37.9
Injection IV	22.0	35.7	52.2	53.7	33.4
Injection V	29.6	40.8	107.6	122.2	134.5

	21 days	28 days	35 days	42 days
Injection I	21.7	13.9	14.6	18.7
Injection II	60.2	58.3	50.3	41.6
Injection III	21.8	21.7	17.8	24.1
Injection IV	32.2	25.3	21.0	23.6
Injection V	101.8	70.1	62.0	45.4

It will be noted from the foregoing table that with Injection I maximum activity is obtained in seven days, whereas with Injection II maximum activity is reached in nine days with a much greater degree of activity; moreover even after 42 days the activity is still in general much higher than is reached at any time with Injection I. Comparison of Injections III and IV shows that the activity of the new derivative (Injection IV) is such that the fraction (one fifth) of the active component present in the Injection IV compared with Injection III gives approximately the same results as with the propionate of Injection III. Comparison of the Injections III and V shows that with the same quantity of active material a still higher peak of activity is reached after fourteen days and that a great measure of activity is preserved even after 42 days.

What we claim is:—

1. A new biologically active compound consisting of testosterone β-phenylpropionate.

2. A method of preparing testosterone β-phenylpropionate comprising reacting testosterone with a halide of β-phenylpropionic acid in the presence of an organic acid acceptor or with the anhydride of β-phenylpropionic acid.

3. A method according to claim 2 using the anhydride of β-phenylpropionic acid wherein the reaction is accelerated by heating at a temperature of the order of 100° C.

4. A method according to claim 3, wherein the reaction is performed in pyridine, benzene or other inert solvent.

5. A method according to claim 2, wherein testosterone is condensed with β-phenylpropionic chloride dissolved in an organic acid-acceptor such as pyridine, or in a mixture of benzene and pyridine containing sufficient pyridine to neutralise the hydrogen chloride liberated by the reaction.

6. Testosterone β-phenylpropionate whenever produced by the methods particularly described and ascertained herein.

7. The methods of producing the testosterone β-phenylpropionate substantially as herein described with reference to the foregoing examples.

BROMHEAD & CO.,
Chartered Patent Agents,
Manfield House,
376—379, Strand, London, W.C.2.

PROVISIONAL SPECIFICATION

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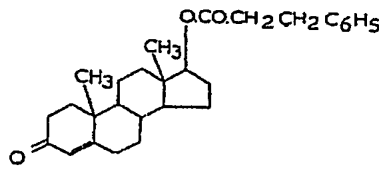
It has now been found that outstandingly successful results are obtained by the hitherto unknown testosterone phenylpropionate. It has been found by experiment that this substance maintains its activity for a much longer period than the simple esters and even than the cyclopentylpropionate or cyclohexylpropionate derivatives and in addition it somewhat surprisingly exhibits a higher degree of activity than either the simple esters or the cyclopentylpropionate and cyclohexylpropionate derivatives. Thus for example the growth of seminal vesicles in castrated rats obtained by injecting testosterone phenylpropionate is equal to that obtained by injecting four times the weight of the propionate and the duration of activity is three to four times as long. The new derivative can be prepared according to the invention by condensing testosterone with phenylpropionic anhydride either alone, in which case the reaction time is shortened by heating, or dissolved in pyridine, benzene or other suitable solvent. It can also be prepared from testosterone and phenylpropionyl chloride in a suitable solvent such as pyridine or a mixture of benzene and pyridine containing sufficient pyridine to neutralise the hydrogen chloride liberated.

The structural formula of the new compound, testosterone phenylpropionate according to the invention is as follows:



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EXAMPLE 3.

To a solution of 10 gms. of testosterone in 30 cc. pyridine is added 12.5 gm. of phenylpropionic anhydride. After standing overnight at room temperature the solution is decomposed by addition of water, and the testosterone phenylpropionate crystallised from methanol melting point 116.5—117° C.

EXAMPLE 4.

To a solution of 10 gms. of testosterone in 30 cc. benzene is added 15 gm of phenylpropionic anhydride. After standing at 15—20° for twenty-four hours the solution is shaken with water and then dilute sodium carbonate solution, dried and distilled to dryness. The product is crystallised from methanol, melting point 116—117°.

EXAMPLE 5.

10 gms. of testosterone and 12.5 gms. of phenylpropionic anhydride are heated together at 100° C. for five hours. The melt is then triturated with water and the solid washed with dilute sodium carbonate solution, dried and crystallised from methanol, melting point 116—117° C.

BROMHEAD & CO.,
Chartered Patent Agents,
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